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DEVICE AND METHOD FOR TREATING RESTENOSIS

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/322,143 filed September 14, 2001, which is hereby incorporated by reference in its entirety herein.

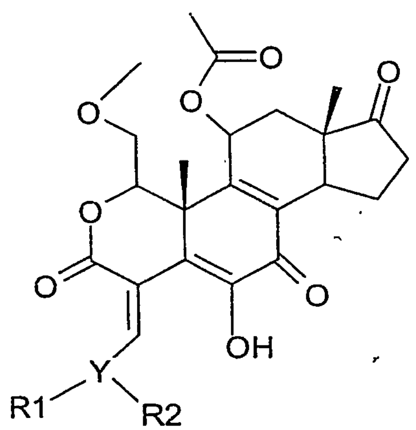
BACKGROUND OF THE INVENTION

Vascular restenosis is a major long-term complication following surgical intervention of blocked arteries by percutaneous transluminal coronary angioplasty (PTCA), atherectomy, laser angioplasty and arterial bypass graft surgery. In about 35% of the patients who undergo PTCA, reocclusion occurs within three to six months after the procedure. The current strategies for treating vascular restenosis include mechanical intervention by devices such as stents or pharmacologic therapies including heparin, low molecular weight heparin, coumarin, aspirin, fish oil, calcium antagonist, steroids, and prostacyclin.

In the pathogenesis of restenosis excessive cell proliferation and migration occurs as a result of growth factors produced by cellular constituents in the blood and the damaged arterial vessel wall that mediate the proliferation of smooth muscle cells in vascular restenosis. Agents that inhibit the proliferation and/or migration of smooth muscle are useful in the treatment and prevention of restenosis. Further, agents that inhibit the inflammatory response of smooth muscle are useful in the treatment and prevention of restenosis. The present invention provides for the use of wortmannin and certain analogs as restenosis inhibitors.

SUMMARY OF THE INVENTION

The invention provides wortmannin analogs useful in the inhibition of restenosis in a subject. The invention is comprised of stents or other devices such as bioprosthetic implants that may be coated with the wortmannin analogs. The present invention is also directed to methods comprised of administering wortmannin analogs to a subject at a pharmaceutically effective dose of a compound. The wortmannin analogs may be any of those described herein, but are preferably selected from the group of consisting of those wortmannin analogs described in Figs 1-3, even more preferably Fig. 2. The wortmannin analogs of the present invention expected to be useful in treating restenosis are represented by the following general chemical formula:



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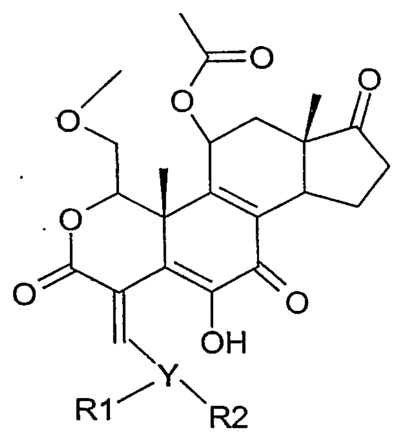


Wherein Y is a heteroatom, preferably N or S, and R1 or R2 are unsaturated alkyl, non-linear alky, branched alky, substituted alkyl or cyclic alkyl.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the basic wortmannin analog structure in accordance with the present invention;

Figure 2 illustrates the structure of certain wortmannin analog structures in accordance with the present invention; and

Figure 3 illustrates the structure of certain other wortmannin analog structures in accordance with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Vascular restenosis after percutaneous transluminal coronary angioplasty (PTCA) has been shown to be a tissue response characterized by an early and late phase. The early phase occurring hours to days after PTCA is due to thrombosis with some vasospasms while the late phase appears to be dominated by excessive proliferation and migration of smooth muscle cells. In this disease, the increased cell motility and colonization by smooth muscle cells and macrophages contribute significantly to the pathogenesis of the disease. The excessive proliferation and migration of vascular smooth muscle cells may be the primary mechanism to the reocclusion of coronary arteries following PTCA, atherectomy, laser angioplasty and arterial bypass graft surgery.

The current invention concerns the discovery that wortmannin analogs that are useful in the inhibition of restenosis. Figure 1 illustrates the general structure of compounds in accordance with the present invention. Figure 2 illustrate specific wortmannin analogs in accordance with the present invention and Figure 3 illustrates certain other wortmannin analogs that may be useful in accordance with the present invention.

The biosynthetic production of wortmannin is well known in the art and the analogs are synthesized from wortmannin. U.S. Patent No. 5,480,906, which is incorporated herein by reference in its entirety describes typical synthetic schemes. Typically, wortmannin is produced

by the fermentation of any one of a number of previously disclosed microorganisms such as Talaromyces wortmannin and Penicillium wortmannin, Myrothecium roridium, and Fusarium. Following fermentation, wortmannin is extracted and purified via known methods. Preferably, wortmannin is microbially synthesized and isolated in substantially pure form from a fermentation culture identified as A24603.1.

Culturing the appropriate strain under submerged aerobic conditions in a suitable culture medium until a recoverable amount of wortmannin is produced produces Wortmannin. Wortmannin can be recovered using various isolation and purification procedures understood in the art.

The medium used to grow the culture can be any one of a number of media. For economy in production, optimal yield, and ease of product isolation, however, preferred carbon sources in large-scale fermentation are glucose and soluble starch such as cornstarch. Maltose, ribose, xylose, fructose, galactose, mannose, mannitol, potato dextrin, methyl oleate, oils such as soybean oil and the like can also be used. Preferred nitrogen sources are enzyme-hydrolyzed casein and cottonseed flour, although pepsinized milk, digested soybean meal, fish meal, corn steep liquor, yeast extract, acid-hydrolyzed casein, beef extract, and the like can also be used.

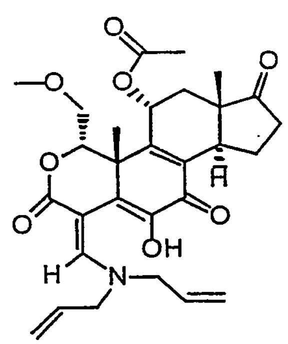
Among the nutrient inorganic salts that can be incorporated in the culture media are the customary soluble salts capable of yielding calcium, magnesium, sodium, ammonium, chloride, carbonate, sulfate, nitrate, zinc, and like ions. Essential trace elements necessary for the growth and development of the organism also should be included in the culture medium. Such trace elements commonly occur as impurities in other substituents of the medium in amounts sufficient to meet the growth requirements on the organism.

For production of substantial quantities of wortmannin, submerged aerobic fermentation in stirred bioreactors is preferred. Small quantities of wortmannin may be obtained by shake-flask culture. Because of the time lag in production commonly associated with inoculation of large bioreactors with the spore form of the organism, it is preferable to use vegetative inoculum. The vegetative inoculum is prepared by inoculating a small volume of culture medium with the spore form or mycelial fragments of the organism to obtain a fresh, actively growing culture of the organism. The vegetative inoculum medium can be the same as that used for larger fermentations, but other media are also suitable.

Following its production, wortmannin can be recovered from the fermentation medium by methods used in the art. The wortmannin produced during fermentation is usually found mainly in the broth. Typically, wortmannin can be recovered from the biomass by a variety of techniques. A preferred technique involves filtering whole fermentation broth with a ceramic filter. The filtrate is eluted with an organic solvent such as ethyl acetate and concentrated. The concentrate is suspended in alcohol until crystallization occurs and the solution is filtered, washed and dried. For confirmation, the crystalline material is dissolved in an organic solvent and chromatographed on a reverse-phase silica gel absorbent (C_8 or C_{18}). Fractions are eluted in an organic-aqueous buffer such as 60% acetonitrile.

Wortmannin may be further manipulated to arrive at the compounds of the present invention. Although the synthesis of particular analogs of wortmannin are illustrated below, other synthetic schemes common in the art will allow one ordinarily skilled in the art to synthesize compounds in accordance with the present invention, and the synthetic schemes set forth herein should, in no way, be considered limiting.

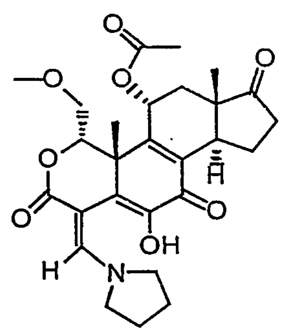
Acetic acid 4-diallylaminomethylene-6-hydroxy-1-α-methoxymethyl-10β,13β-dimethyl-3,7,17-trioxo-1,3,4,7,10,11β,12,13, 14α,15,16,17-dodecahydro-2-oxa-cyclopenta[*a*]phenanthren-11-yl ester (djm2-166).



To a solution of wortmannin (10.7 mg, 25.0 μmol) in CH_2Cl_2 (125 μL) was added a freshly prepared 0.2 M stock solution of diallylamine (138 μL, 27.5 μmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 h. The solvent and excess amine were removed *in vacuo*, and the product was purified via chromatography on SiO_2 (hexanes/ethyl acetate, 1:9) to

give djm2-166 (9.0 mg, 17 μmol, 68%) as an orange oil: $[\alpha]_D$ -630 (*c* 0.0015, CH_2Cl_2, 23 °C); IR (KBr) 3391, 1743, 1695, 1685, 1622, 1569, 1222, 1111, 1100 cm^{-1}; ^1H NMR δ 8.20 (s, 1 H), 6.81 (s, 1 H), 6.06 (dd, 1 H, J = 7.4, 4.8 Hz), 5.85 (br s, 1 H), 5.62 (br, 1 H), 5.44-5.04 (m, 4 H), 4.48 (dd, 1 H, J = 7.2, 1.9 Hz), 4.05-3.60 (m, 4 H), 3.26 (s, 3 H), 3.27-3.20 (m, 1 H), 3.16 (dd, 1 H, J = 10.9, 7.2 Hz), 3.00-2.90 (m, 2 H), 2.59 (dd, 1 H, J = 19.4, 8.6 Hz), 2.40 (dd, 1 H, J = 14.4, 7.7 Hz), 2.35-2.07 (m, 2 H), 2.07 (s, 3 H), 1.83 (dd, 1 H, J = 14.4, 4.7 Hz), 1.54 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR δ 217.0, 178.5, 169.6, 164.8, 156.3, 151.5, 139.0, 136.9, 132.2, 131.3, 127.7 (2 C), 119.2, 89.0, 81.9, 73.1, 67.6, 59.1, 50.9 (2 C), 48.9, 42.3, 42.2, 37.5, 36.0, 24.6, 22.2, 20.8, 16.1; MS (EI) *m/z* (rel. intensity) 525 (M^+, 11), 466 (17), 391 (15), 350 (14), 323 (13), 266 (17), 239 (17), 60 (100); HRMS (EI) calculated for $C_{29}H_{35}NO_8$ 525.2363, found 525.2386.

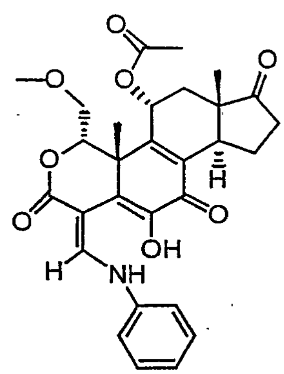
Acetic acid 6-hydroxy-1α-methoxymethyl-10β,13β-dimethyl-3,7,17-trioxo-4-pyrrolidin-1-yl-methylene-1,3,4,7,10,11β,12,13,14α,15,16,17-dodecahydro-2-oxa-cyclopenta[*a*]phenanthren-11-yl (djm2-167).



To a solution of wortmannin (30.0 mg, 70.0 μmol) in CH_2Cl_2 (200 μL) was added pyrrolidine (7.0 μL, 84 μmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 h. The solvent and excess thiol were removed *in vacuo* and the product was purified by chromatography on SiO_2 (hexanes/ethyl acetate 9:1, then 1:1) to give djm2-167 (30.0 mg, 60.6 μmol, 86%) as an orange oil: $[\alpha]_D$ -390 (*c* 0.0073, CH_2Cl_2, 23 °C); IR (KBr) 3337, 1740, 1684, 1617, 1570, 1261, 1221, 1099, 1018 cm^{-1}; ^1H NMR δ 8.29 (s, 1 H), 6.72 (s, 1 H), 6.07 (dd, 1 H, J = 6.9, 4.8 Hz), 4.47 (dd, 1 H, J = 7.0, 1.9 Hz), 3.80-3.70 (m, 2 H), 3.25 (s, 3 H), 3.25-3.14 (m, 2

H), 3.02-2.90 (m, 2 H), 2.69 (br s, 1 H), 2.58 (dd, 1 H, *J* = 19.1, 8.4 Hz), 2.39 (dd, 1 H, *J* = 14.6, 7.8 Hz), 2.32-2.08 (m, 2 H), 2.06 (s, 3 H), 1.99-1.95 (m, 5 H), 1.84 (dd, 1 H, *J* = 14.5, 4.2 Hz), 1.56 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR δ 217.5, 178.9, 169.9, 164.9, 153.9, 151.3, 137.6, 137.1, 129.2, 89.4, 82.1, 73.3, 67.7, 59.3, 55.2, 49.2 (2 C), 42.6, 42.4, 37.8, 36.3, 25.6 (2 C), 24.5, 22.4, 21.0, 16.3; MS (EI) *m/z* (rel. intensity) 499 (M^+, 1), 439 (2), 365 (7), 167 (35), 149 (100); HRMS (EI) calculated for $C_{27}H_{33}NO_8$ 499.2206, found 499.2191.

Acetic acid 4-[(benzylmethylamino)methylene]-6-hydroxy-1α-methoxymethyl-10β,13β-dimethyl-3,7,17-trioxo-1,3,4,7,10,11β,12,13, 14α,15,16,17-dodecahydro-2-oxa-cyclopenta[*a*]phenanthren-11-yl ester (djm2-181).



To a solution of wortmannin (10.7 mg, 25.0 μmol) in of CH_2Cl_2 (125 μL) was added a freshly prepared 0.2 M solution of *N*-methylbenzylamine (185 μL, 37.0 μmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*, and the product was purified by chromatography on SiO_2 (hexanes/ethyl acetate, 1:9) to give djm2-181 (13.3 mg, 24.2 μmol, 97%) as an orange oil: $[\alpha]_D$ -835 (*c* 0.0014, CH_2Cl_2, 23 °C); IR (neat) 1742, 1685, 1618, 1589, 1575, 1224 cm^{-1}; ^{1}H NMR δ 8.36 (br s, 1 H), 7.36-7.27 (m, 5 H), 6.60 (bs s, 1 H), 6.10-6.00 (m, 1 H), 4.68-4.63 (m, 1 H), 4.53-4.47 (m, 2 H), 3.25 (s, 3 H), 3.25-3.11 (m, 2 H), 2.99-2.84 (m, 2 H), 2.71 (br, 2 H), 2.55 (dd, 1 H, *J* = 19.5, 8.9 Hz), 2.38 (dd, 1 H, *J* = 14.4, 7.6 Hz), 2.32-2.05 (m, 2 H), 2.05 (s, 3 H), 1.85 (br s, 1 H), 1.80 (dd, 1 H, *J* = 14.5, 4.7 Hz), 1.52 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR δ 217.3, 178.9, 169.9, 164.7, 158.3, 151.7, 138.8,

137.1, 134.9, 129.0 (3 C), 128.6, 128.1 (2 C), 88.7, 82.2, 73.4, 67.9, 64.3, 59.4, 49.1, 42.7, 42.5, 37.8 (2 C), 36.3, 25.2, 22.5, 21.1, 16.3; MS (EI) *m/z* (rel. intensity) 549 (M^+, 14), 489 (37), 415 (15), 120 (23), 91 (100); HRMS (EI) calculated for $C_{31}H_{35}NO_8$ 549.2363, found 549.2340.

For therapeutic treatment of the specified indications, a wortmannin analog of Figures 1-3 may be administered as such, or can be compounded and formulated into pharmaceutical compositions in unit dosage form for parenteral, transdermal, rectal, nasal, local intravenous administration, or, preferably, oral administration. Such pharmaceutical compositions are prepared in a manner well known in the art and comprise at least one active compound selected from the group consisting of those wortmannin analogs of Figs 1-3 associated with a pharmaceutically carrier. The term "active compound", as used throughout this specification, refers to at least one compound selected from compounds of the formulas or pharmaceutically acceptable salts thereof.

The term "effective amount" as used herein, means an amount of a compound of the present invention that is capable of inhibiting, blocking, or reversing the activation, migration, or proliferation of cells. The activity contemplated by the present methods includes both medical therapeutic and/or prophylactic treatment, as appropriate. The specific dose of a compound administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration, and the condition being treated.

The compounds are effective over a wide dosage range and, for example, dosages per day will normally fall within the range of from 0.001 to 10 mg/kg, more usually in the range of from 0.01 to 1 mg/kg. However, it will be understood that the effective amount administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

The term "inhibiting" includes the administration of a compound of the present invention to prevent the onset of the symptoms, alleviating the symptoms, or eliminating the disease, condition or disorder.

In such a composition, the active compound is known as "active ingredient". In making the compositions, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier that may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid, or liquid material that acts as a vehicle, excipient of medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate alginates, calcium salicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

For oral administration, a compound can be admixed with carriers and diluents, molded into tablets, or enclosed in gelatin capsules. The mixtures can alternatively be dissolved in liquids such as 10% aqueous glucose solution, isotonic saline, sterile water, or the like, and administered intravenously or by injection.

By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The local delivery of inhibitory amounts of active compound for the treatment of restenosis can be by a variety of techniques that administer the compound at or near the proliferative site. Examples of local delivery techniques are not intended to be limiting but to be illustrative of the techniques available. Examples include local delivery catheters, site-specific carriers, implants, coated implants, direct injection, or direct applications. Local delivery by a catheter allows the administration of a pharmaceutical agent directly to the proliferative lesion. Examples of local delivery using a balloon catheter are described in EPO 383 492 A2 and U.S.

Pat. No. 4,636,195 (Wolinsky, Jan. 13, 1987).

Local delivery by an implant describes the surgical placement of a matrix that contains the pharmaceutical agent into the proliferative lesion. The implanted matrix releases the pharmaceutical agent by diffusion, chemical reaction, or solvent activators.

An example of local delivery by an implant is the use of a stent. Stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries. Incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site. Local delivery by this technique is described in Kohn, Pharmaceutical Technology (October, 1990).

Another example is a delivery system in which a polymer that contains the pharmaceutical agent is injected into the lesion in liquid form. The polymer then cures to form the implant in situ. This technique is described in PCT WO 90/03768 (Donn, Apr. 19, 1990).

Another example is the delivery of a pharmaceutical agent by polymeric endoluminal sealing. This technique uses a catheter to apply a polymeric implant to the interior surface of the lumen. The pharmaceutical agent incorporated into the biodegradable polymer implant is thereby released at the surgical site. It is described in PCT WO 90/01969 (Schindler, Aug. 23, 1989).

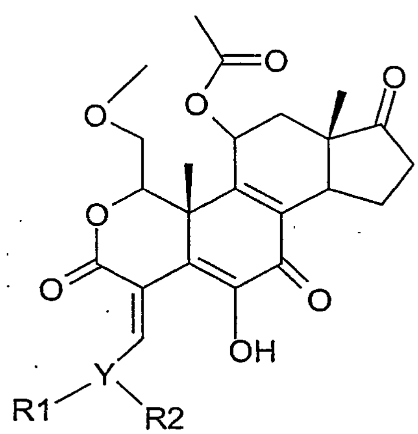
A final example of local delivery by an implant is by direct injection of vesicles or microparticulates into the proliferative site. These microparticulates may be composed of substances such as proteins, lipids, carbohydrates or synthetic polymers. These microparticulates have the pharmaceutical agent incorporated throughout the microparticle or over the microparticle as a coating. Delivery systems incorporating microparticulates are described in Lange, Science 249: 1527-1533 (September, 1990) and Mathiowitz, et al., J. App. Poly. Sci., 26:809 (1981).

Local delivery by site-specific carriers describes attaching the pharmaceutical agent to a carrier that will direct the drug to the proliferative lesion. Examples of this delivery technique include the use of carriers such as a protein ligand or a monoclonal antibody.

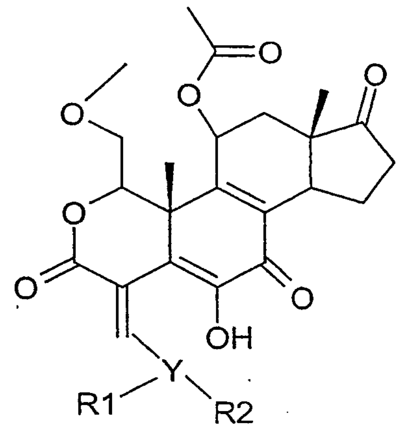
Local delivery by direct application includes the use of topical applications. An example of a local delivery by direct application is applying the pharmaceutical agent directly to the arterial bypass graft during the surgical procedure.

Formulation of wortmannin analogs is well known in the art as is the fermentation

process. The present invention relies on the ordinarily skilled artisan to use those common synthetic and formulation techniques to synthesize compounds of the following general formula:



or



Wherein Y is a heteroatom and R1 or R2 are unsaturated alkyl, non-linear alky, branched alky, substituted alkyl or cyclic alkyl. Preferably, the present invention has a chemical formula corresponding to those shown in Figs 1-3. Even more preferably, the present invention has a chemical formula in accordance with those shown in Fig. 2.

Restenosis is major clinical problem after coronary intervention with coronary stent implantation. In this setting, the smooth muscle that lines the affected coronary artery undergoes hyperplasia and proliferation, due either to transient hypoxia or to an inflammatory response (or a combination of these factors) as a result of the intervention. The proliferation of vascular smooth muscle cells is strongly dependent on the PI 3-kinase – AKT – mTOR signaling pathway. In addition signaling through PI 3-kinase and AKT appears to inhibit apoptosis of smooth muscle cells, which would also increase the mass of the smooth muscle layer in the diseased artery.

The following Table I illustrates the Activity and *in vivo* toxicity of the wortmannin analogues *Enzyme inhibition*

TABLE I

Compound	NSC #	Maximum tolerated dose[e] mg/kg ip qD x 4	PI-3 kinase inhibition IC₅₀ (nM)	mTOR inhibition IC₅₀ (μM)	cytotoxicity NCI cell panel IC₅₀ (μM)	Lymphocyte toxicity relative to wortmannin[b]	Liver toxicity relative to wortmannic[b]	Ratio liver toxicity/ lymphocyte toxicity[d]
wortmannin	221019	2.5	0.3	0.1	8.9	1.0	1.0	1.0
DJM2-166	722134	20 [f]	0.5	>3	2.2	2.2	0.3	0.1
DJM2-167	722135	20	1.1	> 3	0.5	2.4	0.3	0.1
DJM2-168	722136	>20	0.1	> 3	11.9	0.6	0.1	0.2
DJM2-170	722137	9	1.0	> 3	7.1	1.1	1.7	1.5
DJM2-171	722138	6	0.1	> 3	10.2	0.7	1.1	1.6
DJM2-177	722142	6	0.3	1.5	10.2	2.0	0.2	0.1
DJM2-180	722139	>30	10	2.0	8.1	0.5	0.3	0.6
DJM2-181	722140	> 18	0.1	> 3	0.7	1.9	0.2	0.1
DJM2-182	722141	> 18	0.4	> 3	1.0	0.8	0.1	0.1
DJM2-186	722143	> 9	ND	> 3	27.7	0	0.4	>
DJM2-189	722144	>30	5	> 3	21.0	0	0.4	>
DJM2-190	722145	NE	10	> 3	33.0	0.6	NE	NE

ND = not determined, NE = non evaluable insufficient drug
[a] 2 day MTT assay, mean of 60 cell lines
[b] lymphocyte toxicity at the MTD or highest dose tested expressed relative to wortmannin
[c] liver toxicity measured by the % ALT and AST at the MTD or highest dose tested expressed relative to wortmannin
[d] liver toxicity measured relative to wortmannin/decrease in blood lymphocytes relative to wortmannin
[e] MTD = >10% body weight loss
[f] estimated value

The ability of wortmannin and the analogues to inhibit phosphatidylinositol-3-kinase and mTOR is expressed as the dose to cause 50% inhibition (IC_{50}). *Cytotoxicity*-Growth inhibition of human MCF-7 breast cancer cells was measured over 4 days using the MTT assay expressed as the dose to cause 50% inhibition (IC_{50}). *Toxicity* - Groups of 3 C57BL6 mice were administered wortmannin at doses of 1,2 or 3 mg/kg or the analogues at 1, 3, 9 or 18 mg/kg where sufficient compound was available by the intraperitoneal route daily for 4 days. The

animals were killed 24 hr after the last dose and differential blood counts and serum chemistry determined. The major toxicities observed were liver toxicity and lymphocytopenia with decreased red blood cell counts and increased serum glucose at higher doses. Toxicities are measured at the maximum tolerated dose or the highest dose tested Liver toxicity is measured as the mean percent increase in serum ALT and AST expressed relative to wortmannin as 1.0. Lymphocytopenia is expressed as the percent decrease in lymphocyte counts relative to wortmannin as 1.0. A low liver toxicity and a high lymphocyte toxicity as a surrogate for inhibition of tumor cell growth is the desirable feature. Highlighted are the compounds being made for antitumor testing.

Based on the above evidence, it would appear that an inhibitor of PI 3-kinase will inhibit smooth muscle cell growth and survival when impregnated onto the stent device. Moreover, PI 3-kinase inhibitors should also inhibit the local inflammatory response to the implant, which could be favorable factor for long-term stent engraftment or other bioprosthetic implant. In principle, the wortmannin derivatives could be ideal agents for inducing a temporary block of the PI 3-kinase – AKT– mTOR pathway in the local microenvironment surrounding the implanted stent.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.